# Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

# Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

**Oral Solution:**

- [Kaletra] Lopinavir 80 mg/mL and ritonavir 20 mg/mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)

**Film-Coated Tablets:**

- [Kaletra] Lopinavir 100 mg/ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg/ritonavir 50 mg

For additional information, see Drugs@FDA or DailyMed.

## Dosing Recommendations

### Neonate (Aged <14 Days) Dose:

- Lopinavir/ritonavir (LPV/r) is not approved by the Food and Drug Administration (FDA) for use in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. However, when no alternatives are available for neonates who have not met these age thresholds, some members of the Panel would consider using LPV/r oral solution at a dose of 300 mg/75 mg per $m^2$ of body surface area per dose twice daily in combination with careful monitoring of serum osmolality, serum creatinine, liver function enzymes, cardiac function, and electrolytes. This use of LPV/r is based on limited research and clinical experience. The potential benefit of using LPV/r in premature infants must be carefully balanced with the risk of metabolic and cardiac toxicity.

### Dosing for Individuals Who Are Not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

*Infant (Aged 14 Days–12 Months) Dose:*

- Once-daily dosing **is not recommended**.
- LPV/r 300 mg/75 mg per $m^2$ of body surface area per dose twice daily. This approximates LPV/r 16 mg/4 mg (both per kg body weight) twice daily. Use of this dose in infants aged <12 months is associated with lower LPV trough levels than those found in adults; LPV dosing should be adjusted for growth at frequent intervals (see text below). Also see text for information on transitioning infants to the lower mg per $m^2$ dose.

## Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, alteration of taste
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- PR interval prolongation
- QT interval prolongation and Torsades de Pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see Major Toxicities below).

## Special Instructions

- LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. **Do not crush or split tablets**.
- LPV/r oral solution should be administered with food, because a high-fat meal increases absorption.
- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Formulations).
- LPV/r oral solution can be kept at room temperature (up to 77°F or 25°C) if used within 2 months. If kept refrigerated (36°F to 46°F or 2°C to 8°C), LPV/r oral solution remains stable until the expiration date printed on the label.
- Children aged <18 years who receive once-daily dosing of LPV/r have shown

*Child and Adolescent (Aged >12 Months to 18 Years) Dose:*

- Once-daily dosing **is not recommended**.
- LPV/r 300 mg/75 mg per m$^2$ of body surface area per dose twice daily (maximum dose LPV/r 400 mg/100 mg twice daily, except as noted below). For patients weighing <15 kg, this approximates LPV/r 13 mg/3.25 mg (both per kg body weight) twice daily. For patients weighing ≥15 kg to 45 kg, this dose approximates LPV/r 11 mg/2.75 mg (both per kg body weight) twice daily. This dose is routinely used by many clinicians and is the preferred dose for antiretroviral therapy (ART)-experienced patients who could harbor virus with decreased LPV susceptibility (see text below).
- LPV/r 230 mg/57.5 mg per m$^2$ of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients weighing <15 kg, this dose approximates LPV/r 12 mg/3 mg per kg body weight given twice daily. For patients weighing ≥15 kg to 40 kg, this dose approximates LPV/r 10 mg/2.5 mg per kg body weight given twice daily. This lower dose **should not be used** in treatment-experienced patients who could harbor virus with decreased LPV susceptibility.

**Weight-Band Dosing for Lopinavir 100 mg/Ritonavir 25 mg Pediatric Tablets in Children and Adolescents**

| | Recommended Number of LPV/r 100 mg/25 mg Tablets Given Twice Daily | |
|---|---|---|
| **Dosing Target** | 300 mg/m$^2$ per dose given twice daily | 230 mg/m$^2$ per dose given twice daily |
| **Body Weight** | | |
| **15 kg to 20 kg** | 2 | 2 |
| **>20 kg to 25 kg** | 3 | 2 |
| **>25 kg to 30 kg** | 3 | 3 |
| **>30 kg to 35 kg** | 4[a] | 3 |
| **>35 kg to 45 kg** | 4[a] | 4[a] |
| **>45 kg** | 4[a] or 5[b] | 4[a] |

[a] Two tablets that each contain LPV/r 200 mg/50 mg can be substituted for the four LPV/r 100 mg/25 mg tablets in children who are capable of swallowing a larger tablet.

[b] In patients who weigh >45 kg and who are receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV), the FDA-approved adult dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing.

considerable variability in plasma concentrations and have a higher incidence of diarrhea. Therefore, once-daily dosing **is not recommended** for this age group.

- Use of LPV/r once daily is **contraindicated** if three or more of the following LPV resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. This is because higher LPV trough concentrations may be required to suppress resistant virus.

## Metabolism/Elimination

- Cytochrome P450 3A4 substrate and inhibitor.

### Lopinavir/Ritonavir Dosing in Patients with Hepatic Impairment:

- LPV/r is primarily metabolized by the liver. Use caution when administering LPV to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the coformulation of LPV/r, ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

*Adult (Aged >18 Years) Dose:*

- LPV/r 800 mg/200 mg once daily; *or*
- LPV/r 400 mg/100 mg twice daily
- **Do not use** once-daily dosing in children; adolescents; in patients receiving concomitant therapy with NVP, EFV, FPV, or NFV; or in patients with three or more LPV-associated mutations (see Special Instructions for a list of mutations).

**Dosing for Individuals with Three or More Lopinavir-Associated Mutations (See Special Instructions for List):**

- LPV/r 400 mg/100 mg twice daily

**Dosing for Individuals Receiving Concomitant Nevirapine or Efavirenz:**

- These drugs induce LPV metabolism and reduce LPV plasma levels. Increased LPV/r dosing is required with concomitant administration of these drugs. Once-daily dosing **should not be used** in these patients.

*Child and Adolescent (Aged >12 Months to 18 Years) Dose:*

- LPV/r 300 mg/75 mg per $m^2$ of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

*Adult (Aged >18 Years) Dose:*

- The FDA-approved dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing. Once-daily dosing **should not be used**.

**Lopinavir/Ritonavir Used in Combination with Maraviroc**

- Maraviroc doses may need modification (see the Maraviroc section for more information).

***Drug Interactions*** (See also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Lopinavir/ritonavir (LPV/r) is a cytochrome P450 (CYP) 3A4 substrate and inhibitor with the potential for multiple drug interactions. Coadministering LPV/r with drugs that induce CYP3A4 may decrease LPV plasma concentrations, while coadministering LPV/r with other CYP3A4 inhibitors may increase LPV plasma concentrations. Coadministering LPV/r with other CYP3A4 substrates may require dose adjustments and additional monitoring.
- Before initiating therapy with LPV/r, a patient's medication profile should be carefully reviewed for potential drug interactions. In patients treated with LPV/r, fluticasone (a commonly used inhaled and

intranasal steroid) should be avoided, and an alternative steroid should be used. Drug interactions with antituberculous drugs are common; patients who are receiving both LPV/r and antituberculous drugs may need a dose adjustment for LPV/r, or they may need to switch to an antiretroviral (ARV) regimen that does not include LPV/r.

***Major Toxicities***

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, insulin resistance.[1] Hyperlipidemia, especially hypercholesterolemia and hypertriglyceridemia,[2-4] which may be more pronounced in girls than in boys.[5] LPV requires a higher dose of ritonavir (RTV) than some other protease inhibitors (PIs); this higher dose may exacerbate these adverse events (AEs).
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, hepatitis (which has been life-threatening in rare cases). PR interval prolongation, QT interval prolongation, and Torsades de Pointes may occur.
- *Special populations—neonates:* An increased risk of toxicity in premature infants has been reported, including cases of transient symptomatic adrenal insufficiency,[6,7] life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy),[8-10] lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be caused by the drug itself and/or from the inactive ingredients in the oral solution, which include propylene glycol 15.3% and ethanol 42.4%.[10] Transient asymptomatic elevation in 17-hydroxyprogesterone levels has also been reported in term newborns treated at birth with LPV/r.[6] The pharmacokinetics (PKs) and safety of LPV/r were studied in IMPAACT P1106, an opportunistic, multi-arm, Phase 4 prospective study in newborns who received antiretroviral (ARV) and anti-tuberculosis medicines in clinical care. A total of 25 neonates with HIV were enrolled, with a median birth weight of 2,130 g (interquartile range [IQR] 1,775–2,630 g) and a median gestational age of 35 weeks (IQR 32–37 weeks). Neonates received LPV/r solution at a dose of 300 mg/75 mg per $m^2$ twice daily, which was well tolerated and not associated with any treatment-related AEs, even in 13 newborns who initiated therapy prior to 42 weeks postmenstrual age at a mean postnatal age of 37 days (range 13–61 days).[11]

***Resistance***

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

***Pediatric Use***

*Approval*

LPV/r is approved by the Food and Drug Administration (FDA) for use in children, including neonates who have attained a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. However, when no alternatives are available for neonates who have not met these age thresholds, some members of the Panel would consider using LPV/r oral solution at a dose of 300 mg/75 mg per $m^2$ of body surface area per dose twice daily in combination with careful monitoring of serum osmolality, serum creatinine, liver function enzymes, cardiac function, and electrolytes. This use of LPV/r is based on limited research and clinical experience. The potential benefit of using LPV/r in premature infants must be carefully balanced with the risk of metabolic and cardiac toxicity. In pediatric patients receiving LPV/r at a dose of 300 mg/75 mg per $m^2$ twice daily, lower LPV exposure has been observed in infants aged <6 weeks relative to older children.[12]

*Efficacy*

Clinical trials involving ART-naive adults have shown that regimens that contain LPV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) are comparable to a variety of other regimens, including regimens that contain atazanavir, darunavir (DRV), fosamprenavir (FPV), saquinavir/ritonavir, or efavirenz (EFV). Studies have also shown that regimens that contain LPV/r plus two NRTIs are superior to regimens that contain nelfinavir (NFV) and inferior to regimens that contain DRV.[13-21]

LPV/r has been studied in both ARV-naive and ARV-experienced children and has demonstrated durable virologic activity and acceptable toxicity.[22-30]

### *Pharmacokinetics*

#### *General Considerations*

Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The directly scaled dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 $m^2$. For the adult dose of LPV/r 400 mg/100 mg, the scaled pediatric dose would be approximately LPV/r 230 mg/57.5 mg per $m^2$ of body surface area. However, younger children have enhanced LPV clearance and need higher doses to achieve LPV exposures that are similar to those seen in adults treated with standard doses. To achieve a $C_{trough}$ similar to that observed in adults, the pediatric dose needs to be increased 30% over the dose that is directly scaled for body surface area. LPV exposures in infants[12,24,29] are compared to those in older children[22] and adults[31] in Table A below.

**Table A. Pharmacokinetics of Lopinavir/Ritonavir by Age**

| PK Parameters | Adults (n = 19)[31] | Children (n = 12)[22] | Children (n = 15)[22] | Infants[a] at 12 Months (n = 20)[29] | Infants at 6 Weeks–6 Months (n = 18)[24] | Infants at 14 Days to <6 Weeks (n = 9)[12] |
|---|---|---|---|---|---|---|
| **LPV Dose** | 400 mg | 230 mg/$m^2$ | 300 mg/$m^2$ | 300 mg/$m^2$ | 300 mg/$m^2$ | 300 mg/$m^2$ |
| **$AUC_{0-12}$ (mcg·hr/mL)** | 92.6 | 72.6 | 116.0 | 101.0 | 74.5 | 43.4 |
| **$C_{max}$ (mcg/mL)** | 9.8 | 8.2 | 12.5 | 12.1 | 9.4 | 5.2 |
| **$C_{trough}$ (mcg/mL)** | 7.1 | 4.7 | 7.9 | 4.9 | 2.7 | 2.5 |
| **$C_{min}$ (mcg/mL)** | 5.5 | 3.4 | 6.5 | 3.8 | 2.0 | 1.4 |

[a] This column contains unreported data that were originally generated for a published study. The data were provided by Edmund Capparelli, PharmD in a personal communication (April 18, 2012).

**Note:** Values are means; all data comes from studies where none of the participants received NNRTIs as part of their ART.

**Key:** ART = antiretroviral therapy; AUC = area under the curve; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitors; PK = pharmacokinetic

Models suggest that diet, body weight, and postnatal age are important factors in LPV PKs, with improved bioavailability as dietary fat increases during the first year of life[32] and with clearance slowing by age 2.3 years.[33] A study from the United Kingdom and Ireland compared outcomes of LPV/r treatment with either 230 mg per $m^2$ of body surface area per dose or 300 mg per $m^2$ of body surface area per dose in children aged 5.6 to 12.8 years at the time of LPV/r initiation. The findings suggested that the higher dose was associated with improved long-term viral load suppression.[34]

### *Pharmacokinetics and Dosing*

#### *14 Days to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)*

The PKs of the oral solution at approximately LPV/r 300 mg/75 mg per $m^2$ of body surface area per dose twice daily was evaluated in infants aged <6 weeks[12] and infants aged 6 weeks to 6 months.[24] Even at this higher dose, $C_{trough}$ levels were highly variable, but they were lower in infants than in children aged >6 months. $C_{trough}$ levels were lower in infants aged ≤6 weeks than in infants aged 6 weeks to 6 months. By age 12 months, LPV area under the curve (AUC) was similar to that found in older children.[29] Because infants grow rapidly in the first months of life, it is important to optimize LPV dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg per $m^2$ of body surface area in older children and adolescents,[25] some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg per m$^2$ of body surface area dose to allow for projected growth between clinic appointments.

*12 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)*

Lower trough concentrations have been observed in children receiving LPV/r 230 mg/57.5 mg per m$^2$ of body surface area per dose twice daily than in children receiving LPV/r 300 mg/75 mg per m$^2$ of body surface area per dose twice daily (see Table A above).[21] Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using LPV/r 300 mg/75 mg per m$^2$ of body surface area per dose twice daily (when LPV/r is given without nevirapine [NVP], EFV, FPV, or NFV), rather than the FDA-approved dose of LPV/r 230 mg/57.5 mg per m$^2$ of body surface area per dose twice daily.

For infants receiving LPV/r 300 mg/75 mg per m$^2$ of body surface area per dose twice daily, immediate dose reduction at age 12 months **is not recommended**; many practitioners would allow patients to "grow into" the LPV/r 230 mg/57.5 mg per m$^2$ of body surface area per dose twice daily dose as they gain weight over time. Some practitioners would continue the infant dose (LPV/r 300 mg/75 mg per m$^2$ of body surface area per dose twice daily) while using the LPV/r liquid formulation.

*Pharmacokinetics and Dosing with Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir*

In both children and adults, the LPV $C_{trough}$ is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or concomitant FPV or NFV. Higher doses of LPV are recommended when the drug is given in combination with NVP, EFV, FPV, or NFV. In 14 children who were treated with LPV/r 230 mg/57.5 mg per m$^2$ of body surface area per dose twice daily plus NVP, the mean LPV $C_{trough}$ was 3.77 ± 3.57 mcg/mL.[22] Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/r, the variability in concentration is much higher in children than in adults.[22,35] In a study of 15 children with HIV aged 5.7 to 16.3 years who were treated with LPV/r 300 mg/75 mg per m$^2$ of body surface area per dose twice daily plus EFV 14 mg/kg body weight per dose once daily, there was a 34-fold interindividual variation in LPV trough concentrations. Five of 15 children (33%) had LPV 12-hour trough concentrations that were <1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.[36] A PK study in 20 children aged 10 to 16 years who were treated with LPV/r 300 mg/75 mg per m$^2$ of body surface area twice daily plus EFV 350 mg per m$^2$ of body surface area once daily reported only one patient (6.6%) with subtherapeutic LPV trough concentrations,[37] perhaps because the trial used an EFV dose that was approximately 11 mg/kg body weight[37] instead of the 14 mg/kg body weight dose used in the trial discussed above.[36]

### *Dosing*

*Once Daily*

A single daily dose of LPV/r 800 mg/200 mg is approved by the FDA for treatment of HIV in treatment-naive adults aged >18 years. However, once-daily administration **cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM)**; once-daily administration may be successful in select, closely monitored children.[38] There is high interindividual variability in drug exposure for LPV/r, and trough plasma concentrations may fall below the therapeutic range for wild-type virus, as demonstrated in studies of ARV-naive children and adolescents.[39-42] The currently available tablet formulation of LPV/r has lower variability in trough levels than the previously used soft-gel formulation.[42,43] An international, randomized, open-label trial attempted to demonstrate that once-daily LPV/r dosing was noninferior to twice-daily LPV/r dosing in children and adolescents with HIV. This trial was unsuccessful, as a greater number of children and adolescents who received once-daily doses had viral loads ≥50 copies/mL within 48 weeks.[44]

*Dosing and Its Relation to Efficacy*

LPV/r is effective in treatment-experienced patients with severe immune suppression,[45,46] although heavily pre-treated patients may be slower to reach undetectable viral loads[46,47] and may have less-robust CD4 T lymphocyte (CD4) percentage responses.[48]

The relationship between LPV exposure and the susceptibility of the HIV-1 isolate ($EC_{50}$) is a key component of successful treatment. The ratio of $C_{trough}$ to $EC_{50}$ is called the inhibitory quotient (IQ), and in both adults and children treated with LPV/r, viral load reduction is more closely associated with IQ than with either $C_{trough}$ or $EC_{50}$ alone.[49-51] One study investigated the use of the IQ as a guide for therapy by administering higher doses of LPV/r to children and adolescents until a target IQ of 15 was reached. This study showed that doses of LPV/r 400 mg/100 mg per $m^2$ of body surface area per dose twice daily (without FPV, NFV, NVP, or EFV) and LPV/r 480 mg/120 mg per $m^2$ of body surface area per dose twice daily (with NVP or EFV) were safe and tolerable.[25] Results of a modeling study suggest that standard doses of LPV/r may be inadequate for treatment-experienced children and suggest the potential utility of TDM when LPV/r is used in children who were previously treated with PIs.[52] An LPV plasma concentration of ≥1 mcg/mL is cited as a minimum target trough concentration,[53-55] but this concentration may not adequately control viremia in patients with multiple LPV resistance mutations.[56,57]

### ***Formulations***

#### *Palatability*

The poor palatability of the LPV/r oral solution can be a significant challenge to medication adherence for some children and families. Numbing the taste buds with ice chips before or after administering the solution, masking the taste of the solution by administering it with sweet or tangy foods (e.g., chocolate syrup, peanut butter), or having the pharmacist flavor the solution prior to dispensing it are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.[58,59]

#### *Do Not Use Crushed Tablets*

LPV/r tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduced AUC, $C_{max}$, and $C_{trough}$ compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets cannot be recommended for use.[60] In a PK study that used a generic adult formulation of LPV/r manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate LPV $C_{trough}$ measurements.[43]

### ***Toxicity***

Children treated with LPV/r may have less-robust weight gain and smaller increases in CD4 percentage than children treated with NNRTI-based regimens.[27,61-65] However, one study did not observe this difference in the effect of LPV/r on CD4 count,[66] and another study found that the difference did not persist after a year of therapy.[30] Some studies found no differences between the weight gain of children treated with LPV/r and those treated with EFV.[64,67] Switching to an EFV-based regimen at or after age 3 years removed the risk of LPV-associated metabolic toxicity, with no loss of virologic control (see Table 16 in Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy).[64,65] Bone mineral density improved when children were treated with EFV-containing regimens instead of regimens that contained LPV/r.[68]

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